FACULDADE DE MEDICINA
UNIVERSIDADE DO PORTO

MESTRADO INTEGRADO EM MEDICINA

2012/2013

Maria Inês Gomes da Rocha Couto

Depression and anxiety following bilateral deep brain stimulation in Parkinson's disease

março, 2013

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UNIVERSIDADE DO PORTO

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Mestrado Integrado em Medicina

Área: Neurologia

Trabalho efetuado sob a Orientação de:

Dr. João dos Santos Massano de Carvalho

E sob a Coorientação de:

Doutor Nuno Miguel de Sousa Lunet

Trabalho organizado de acordo com as normas da revista:

Movement Disorders: official journal of the Movement Disorder Society

março, 2013

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Projeto de Opção do 6º ano – DECLARAÇÃO DE REPRODUÇÃO

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Título da Dissertação/~~Monografia~~ (cortar o que não interessa):

Depression and anxiety following bilateral deep brain stimulation in Parkinson's disease

Orientador:

Dr. João dos Santos Massano de Carvalho

Coorientador (se aplicável):

Doutor Nuno Miguel de Sousa Lunet

Ano de conclusão: 2013

Designação da área do projeto:

Neurologia

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Faculdade de Medicina da Universidade do Porto, 02/04/2013

Assinatura: Maria Inês Gomes da Rocha Couto

Agradeço a título profissional a orientação do Dr. João Massano e a co-orientação do Doutor Nuno Lunet sobretudo na idealização dos sucessivos melhores caminhos a tomar. Agradeço, ainda, à Drª Ana Monteiro e à Drª Ana Oliveira pelo trabalho desenvolvido sem o qual não teria sido possível rever tão a fundo a literatura. Obrigado.

À minha irmã, por tudo.
À minha irmã, por tudo.
À minha irmã, por tudo.
E mais houvesse. Obrigado! Pela paciência, conselhos, cafés, maledicências da vida, simples companhia. Sobretudo, por ser eu a felizarda de anteceder um ser tão grande na progénie.

Posto isto, aos meus pais pelo gene da procura da batalha mais difícil. É *dominante* entre nós essa tendência! A trivialidade não faz diferente nem maior nem mais além. E sem isso nada muda. E o estagnado é vazio e sem desafio ao intelecto e às capacidades.

À minha avó pela bendita costela, porque afinal se não nos rirmos da vida também não a levamos muito avante nem a sério o suficiente para percebermos as suas ironias.

À Vera! Que tanto aturou. E que ajudou ainda mais. Muito obrigado. Pelos cafés, pela última mesa da biblioteca, pelos infindáveis relambórios (e o semáforo verde, e vermelho, e verde, e vermelho...), por alguns dos não muitos sorrisos dos últimos tempos, pelo feitio (haja alguém que compreende que realmente a responsabilidade por vezes enerva!). Obrigado.

Todas as palavras de alento de todas as pessoas amigas.

Obrigado.

Title
Depression and anxiety following bilateral deep brain stimulation in Parkinson's disease

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Word Count: 2435

Running title
Depression and anxiety following DBS in PD

Key words
Parkinson's disease; deep brain stimulation; anxiety; depression; systematic review

Financial disclosures: Maria Inês Couto declares no conflicts of interest.

Funding sources: This work received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Abstract

Background: Deep brain stimulation (DBS) is an effective therapy in advanced Parkinson's disease (PD), improving motor symptoms, motor complications and quality of life. However, adverse psychiatric outcomes have been reported by several authors, albeit variably and in an unstandardized fashion. We aimed to summarize the published evidence on the outcomes of anxiety and depressive symptoms in PD patients following DBS, through systematic review and meta-analysis.

Methods: Pubmed was searched until May 2012 to identify studies that assessed anxiety and depressive symptoms in PD patients who underwent bilateral DBS of the subthalamic nucleus (STN) or globus pallidus internus (GPi). Random effects meta-analyses were conducted for groups of at least three studies that were homogeneous regarding the design and the instruments used.

Results: Depression and anxiety improvement is apparent after DBS, more pronounced in the short-term, an effect that seems to wane in later assessments. Concerning depression, STN-DBS shows superiority against medical treatment, but not when compared to eligible for surgery control groups. The opposite is apparent for anxiety, as results favor medical treatment over STN-DBS, and STN-DBS over eligible for surgery control group. Superiority of one target over the other is not evident from the results, but data slightly favors GPi for both outcomes.

Conclusions: No clear conclusion can be drawn from this meta-analysis, with the possible exception of depression improvement at short-term following STN-DBS, although with significant heterogeneity of results. Efforts should be carried out to standardize assessment procedures for depression and anxiety in PD patients undergoing DBS.

Introduction:

Parkinson's disease (PD) is a frequent, disabling neurodegenerative condition characterized by motor and non-motor symptoms, including cognitive and behavioral[1]. Deep brain stimulation (DBS) has proved effective in advanced PD, as motor symptoms, fluctuations, disability and quality of life improve in patients carefully selected for the procedure[2-4]. Recently, the efficacy of DBS has been also demonstrated in PD with early motor complications[5], suggesting that the universe of potential surgical candidates is wider than previously established. However, significant concerns have been raised about potential cognitive and psychiatric adverse effects in PD patients following DBS, and some data even suggested that consequences might vary according to the chosen target, namely the subthalamic nucleus (STN) or the globus pallidus internus (GPi)[6-8]. On the other hand, several studies found no significant adverse psychiatric outcomes following DBS in PD[9-11]. This issue remains incompletely clarified, as several different assessment methods have been used, and results have been reported under diverse formulas. Data have been reviewed systematically in two previous publications concerning psychiatric outcomes in patients undergoing bilateral DBS, but one study published in 2006 was limited to patients having STN-DBS[12], while the other, published in 2007, jointly analyzed results in several pathologies including PD[13]; in addition, several other studies in PD have been published since then, thus justifying re-appraisal of findings. We aimed at systematically reviewing the literature and summarizing the evidence by meta-analysis, in order to establish state of the art knowledge concerning anxiety and depression following DBS in PD.

Methods:

PubMed was searched from inception until May 2012, using the search expression "("deep brain stimulation" OR "subthalamic stimulation" OR (stimulation AND ("subthalamic nucleus" OR "globus pallidus"))) AND (parkinson disease OR parkinson's disease)", to identify studies that assessed anxiety and depressive symptoms in PD patients who underwent bilateral DBS.

A total of 3276 references were screened by one of three reviewers (MIC, AM, AO), following the same exclusion criteria defined a priori, as follows: 1) language other than English, Portuguese and Spanish; 2) non-human data; 3) disorders other than PD; 4) studies not concerning DBS; 5) studies not conveying original data (reviews, systematic reviews, meta-analysis, book chapters, letters to the editor with no original data); 6) case reports; and 7) reports with no data on the outcomes of interest, namely: 7.1) no clinical outcome at all (e.g. image methods for target location); 7.2) clinical outcome other than psychiatric; 7.3) psychiatric outcome not objectively assessed by psychometric instrument. References were then restricted to those reporting on the most relevant DBS targets in PD (STN and GPi), and depression or anxiety only. In addition, study design details were used to exclude studies not enrolling participants consecutively or randomly selected. Duplicate references were eliminated by comparing titles, authors, centers and sample details, and a total of 63 reports[3,10,14-74] were considered for the systematic review. The systematic review flow-chart is presented as appendix 1.

Quantitative data on depression and anxiety were collected from the eligible studies along with DBS target and follow-up time. Five aspects were considered in order to group and analyze data: 1) *Main outcome*: depression or anxiety; 2) *DBS target*: STN and GPi were individually considered, so studies containing indiscriminate information on both targets[3,72] have not been analyzed; 3) *Follow-up time*: three main periods were considered: up to 6 months after surgery (short-term follow-up); between 6 months and 3 years (mid-term follow-up); and more than 3 years (long-term follow-up); within each defined time period we selected the data referring to the longest follow-up for analysis, whenever data was available for different moments after the intervention; 4) *Assessment scale(s)* employed; 5) *Study design*: two main types of information were sought: the change of variables of interest with the exposure to the procedure (follow-up studies with pre- and post-operative data) and the difference between groups concerning the response to DBS (studies with different types of comparators). DBS *versus* controls and STN-DBS *versus* GPi-DBS were considered comparisons of interest, so in studies with other comparators, only the information concerning the DBS group was collected. "On" state evaluation was considered in studies reporting "on" *versus* "off" state comparison. In partial duplicates with patients overlapping but with different assessment scales[35,49], follow-up time[16,27] or comparison groups[73], a selection of relevant data was performed for each one, and only specific duplicated information was excluded. A total of 63 studies assessing depression and/or anxiety following DBS (STN or GPi) in consecutive samples of PD patients were selected for analysis.

Forest-plots were used to summarize the findings from all eligible studies and random effects meta-analysis (DerSimonian and Laird method) was performed for groups of at least three comparable studies. The I^2 statistic was used to quantify heterogeneity. Original data concerning different strata from the same studies were assumed as different samples, strata being defined by age[43], single or multiple recording electrodes[40], and center (in one collaborative study)[73]. The pre to postoperative variation was calculated from "postop score – preop score". Differences between STN-DBS and the comparison groups were calculated by "STN score – comparator score". The effect size (ES) and corresponding 95% confidence interval (CI) were extracted whenever provided in the original reports or computed using the published data considering matched and independent samples, respectively (adopted formulas detailed in appendix 2). Test-retest coefficients have been collected for the several psychometric instruments[75-86].

Results:

Nearly all studies (n=62, 98.4%) provided data on depression, and 24 (38.1%) on anxiety assessment scales. STN-DBS was performed in 60 studies (95.2%) and GPi-DBS in 9 (14.3%); the overlap between target groups corresponds to STN *versus* GPi comparison studies. Two additional reports[3,72] that did not discriminate data by target were not considered in our analysis. From the remaining 61 references, short-term evaluation was performed in 37 (60.7%), mid-term in 36 (59.0%) and long-term in 5 (8.2%). Data on pre- to postop variation was available in 57 (93.4%) reports and 16

(26.2%) presented STN-DBS *versus* different comparison groups: the comparators were groups of patients submitted to GPi-DBS (4 studies, 25%), eligible for surgery (EFS) (6 studies, 37.5%) and medical treatment (MT) (7 studies, 43.8%). Information on target, study design, assessment scales and follow-up time in each individual study is detailed in appendix 2. Ten studies presented non-comparable information, so data presented in a quantitative and comparable way from the remaining 52 studies were analyzed henceforward.

1) Depression:
   a) Pre – postop variation:
      i) STN-DBS (figures 1 and 2):
         (1) Short-term follow-up: meta-analysis was performed on Beck Depression Inventory (BDI), Hamilton Depression Rating Scale (HDRS) and Montgomery-Åsberg Depression Rating Scale (MADRS) data. Summary effect size (ES) regarding BDI samples pointed to improvement (-3.05, I^2=68.8%). Slight improvement occurred in HDRS group (ES=-0.286, I^2=70.5%) and MADRS group (ES=-0.763, I^2=0%). All the remaining scales showed improvement.
         (2) Mid-term follow-up: meta-analysis was performed on BDI and MADRS data only, with summary ES showing very slight improvement, along with high heterogeneity of the results: -0.37 (I^2 72.1%) and -0.636 (I^2 79.1%), respectively. Both Zung Self-Rating Depression Scale (Zung-d) and one of the HDRS samples showed improvement. In the remaining, depression levels worsened after surgery.
         (3) Long-term follow-up: meta-analysis was performed only on BDI data. Summary ES indicated very slight depression improvement: -0.222 (I^2 40.9%). Additionally, the Zung-d sample showed improvement and the remaining Hospital Anxiety and Depression Scale – depression part (HAD-d) sample worsened.
      ii) GPi-DBS (figure 3):
         (1) Short-term follow-up: meta-analysis was conducted for BDI data and summary ES revealed depression improvement, despite heterogeneity was high (summary ES=-3.101, I^2 57.9%). The remaining groups showed improvement as well.
         (2) Mid-term follow-up: depression, as assessed by the several instruments, improved in all the samples.
   b) STN *versus* comparator (figure 4):
      i) MT group:
         (1) Short-term follow-up: two samples (assessed with MADRS and Zung-d) showed a trend towards medical treatment superiority. The remaining five favored STN-DBS.
         (2) Mid-term follow-up: both groups favored STN-DBS.

ii) EFS group:
(1) Short-term follow-up: in this single MADRS sample, medical treatment was superior.
(2) Mid-term follow-up: two samples (BDI and MADRS) slightly favored STN-DBS. The remaining three samples (from HAD-d and also BDI and MADRS groups) pointed to medical treatment superiority, a tendency that is stronger in HAD-d sample.

iii) GPi group:
(1) Short-term follow-up: one BDI sample favored STN and the other one, along with the HDRS sample, favored GPi-DBS.
(2) Mid-term follow-up: both BDI samples showed GPi-DBS superiority. Conversely, in the HDRS sample, STN-DBS was superior.

2) Anxiety
a) Pre – postop variation:
i) STN-DBS (figure 5):
(1) Short-term follow-up: one single sample from State and Trait Anxiety Inventory – Trait part (STAI-t) group revealed anxiety worsening following STN-DBS, with all the remaining studies showing improvement after the intervention.
(2) Mid-term follow-up: meta-analysis was performed on State and Trait Anxiety Inventory – State part (STAI-s) and STAI-t data. Summary ES demonstrated slight anxiety improvement in STAI-s group and moderate worsening in STAI-t group: -0.930 (I^2 0%) and 1.595 (I^2 64.2%), respectively. Hospital Anxiety and Depression Scale – Anxiety part (HAD-a) single sample showed worsening. The remaining samples presented anxiety improvement.
(3) Long-term follow-up: STAI-t single sample showed no change. Additionally, one sample assessed by HAD-a worsened and the remaining two (STAI-s and Zung-a groups) improved.

ii) GPi-DBS (figure 3):
(1) Short-term follow-up: the only existing sample performed Beck Anxiety Inventory (BAI) and anxiety seemed to improve.
(2) Mid-term follow-up: the only existing sample performed STAI-s and STAI-t and both improved.

b) STN *versus* comparator (figure 4):
i) MT group:
(1) Short-term follow-up: the single BAI sample results favored STN-DBS. The remaining groups apparently showed medical treatment superiority.

ii) EFS group:
(1) Short-term follow-up: the only existing sample performed Association for Methodology and Documentation in Psychiatry – Anxiety part (AMDP-AT) and the results favored STN-DBS.

(2) Mid-term follow up: one sample from STAI-s group favored medical treatment. The remaining two samples (from HAD-a and STAI-t groups) pointed towards STN-DBS superiority.

iii) GPi group:

(1) Mid-term follow-up: the only existing sample revealed GPi-DBS superiority, as assessed by the STAI-s and STAI-t.

Discussion:

Overall, objectively assessed depression and anxiety apparently improve after DBS, with effects being more pronounced in the short-term, and becoming weaker when follow-up is longer. Nonetheless, results are highly heterogeneous, both across studies and psychometric instruments. Concerning depression, STN-DBS shows superiority against medical treatment, but not when compared to eligible for surgery control groups, especially in the short-term. The opposite occurs for anxiety, as results favor medical treatment over STN-DBS, and STN-DBS when compared with eligible for surgery control group. Superiority of one target over the other is not evident from the results, due to significant heterogeneity of findings and paucity of studies, but data slightly favors GPi for both outcomes.

Among the included comparison studies, two clinical trials on STN-DBS *versus* MT and STN-DBS *versus* GPi-DBS were found. Witt and coworkers[10] conducted a randomized multicenter clinical trial comparing best medical treatment (BMT) and bilateral STN-DBS, with depression and anxiety assessments as specific secondary outcomes. They concluded in favor of DBS safety at short-term follow-up (6 months), in carefully selected patients. The authors adopted “major psychiatric illness—such as a history of or current psychosis or a history of or current severe depression diagnosed by a psychiatrist” as exclusion criteria. A recent randomized multicenter clinical trial compared STN-DBS and GPi-DBS[25], and the authors found a modest difference between the two groups favoring GPi-DBS with regard to depression. The results from both randomized studies conform to our general findings.

The present work focused on depression and anxiety following bilateral DBS in PD, objectively assessed by psychometric instruments. In many of the excluded references, information was reported on DBS side effects (including psychiatric), without a standard definition of the clinical outcomes (concepts such as "slight disturbance of humor" or "mild depression" without further specification are hardly comparable). Additionally, this type of result contains no reference to the potential amelioration of any preoperative mild depressive symptoms following DBS. Therefore, in the present systematic review, the evaluation of the overall depression and anxiety levels following DBS was intended.

One might wonder about possible bias related to dropouts by suicide, since postoperative outcomes would then be wrongly estimated[10,24,25,29,31,61]. However, a large multicenter study[87] found that the completed suicide rate following subthalamic DBS in PD is less than 0.5%, suggesting that any suicide occurrences are unlikely to influence data in this regard.

We found that there are no long-term studies comparing the several therapeutic strategies for PD that adequately report objective data concerning anxiety and depression. Moreover, no long-term studies approaching this issue in GPi-DBS were found, and even short- and mid-term information regarding this target relies only in a few published studies. Therefore, there is a clear imbalance between the number of studies published in STN or GPi reporting objective psychometric data, thus limiting the strength of any comparative analysis. Measuring the outcome of either target could be important, since it has been suggested that patients undergoing either STN-DBS or GPi-DBS might fare differently with regard to mood following surgery[25]. This could be important in order to tailor the procedure (i.e. target choice) for each patient, considering the individual profile of psychiatric symptoms.

The conclusions of the present systematic review are naturally limited by the small amount and specificities of the available publications, namely taking into account that most of the investigations do not have a comparator, and the heterogeneity of methods and presentation of the findings. Another issue identified by this systematic review is the wide range of psychometric instruments used in the setting of DBS in PD, with a total of 11 scales for depression and 10 for anxiety, considering those with quantitative and comparable results only. Thorough analysis of available psychometric instruments might contribute to the rationalization of the choice of scales to use, by narrowing the number of options. For example Williams and collaborators have recently studied 9 depression assessment scales and concluded that any of those is valid, provided that PD-specific cutoff values are used. Anyway, the authors concluded that the 30-item Geriatric Depression Scale could be the most sensible choice in PD[88].

In summary, no definitive conclusions can be drawn from this meta-analysis, with the possible exception that the available data suggests that depression improves following STN-DBS at short-term, although heterogeneity of published results is significant. Our findings are consistent with the notion that DBS is a safe procedure with regard to depression and anxiety, regardless of the target chosen. It seems clear that organized scientific efforts should be carried out in order to reach consensus and issue recommendations on the use of a small number of validated scales that would allow proper assessment and reporting of data concerning depression and anxiety following DBS in PD.

Acknowledgment: Author thanks to Drª Ana Monteiro, Drª Ana Oliveira and the several libraries and authors that helped in references obtaining.

Author roles:
1. Research project: A. Conception, B. Organization, C. Execution;
2. Statistical Analysis: A. Design, B. Execution, C. Review and Critique;
3. Manuscript Preparation: A. Writing of the first draft, B. Review and Critique;
4. Research supervision

Maria Inês Couto: 1A, 1B, 1C, 2A, 2B, 2C, 3A, 3B

Financial disclosure: none. Maria Inês Couto declares no conflicts of interest.

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Figures legends:

Figure 1. Beck Depression Inventory forest-plot (STN-DBS). Beck Depression Inventory results following subthalamic stimulation (STN-DBS) with data grouped and analyzed by follow-up time periods. Effect size and 95% confidence interval are presented for each sample. Overall measure is presented for each time period.
Abbreviations: country abbreviations according to ISO 3166-1 decoding table.

Figure 2. Depression psychometric scales forest-plot (STN-DBS). Depression assessment results following subthalamic stimulation (STN-DBS) with data grouped and analyzed by psychometric instrument and sorted by ascending follow-up time. Effect size and 95% confidence interval are presented for each sample.
Abbreviations: BRMES: Bech-Rafaelsen Melancholia Scale; BSId: Brief Symptom Inventory – depression part; GDS: Geriatric Depression Scale; HADd: Hospital Anxiety and Depression scale – depression part; HDRS: Hamilton Depression Rating Scale; MADRS: Mongomery-Åsberg Depression Rating Scale; POMSd: Profile Of Mood States – depression part; SCL90Rd: Symptom CheckList 90 Revised – depression part; UPDRS I,3: Unified Parkinson's Disease Rating Scale, Part I, Item 3; Zungd: Zung self-rating depression scale. Country abbreviations according to ISO 3166-1 decoding table.

Figure 3. Pallidal stimulation outcomes forest-plot. Depression and anxiety assessment results following pallidal stimulation with data grouped and analyzed by psychometric instrument and sorted by ascending follow-up time. Effect size and 95% confidence interval are presented for each sample.

Abbreviations: BAI: Beck Anxiety Inventory; BDI: Beck Depression Inventory; HDRS: Hamilton Depression Rating Scale; POMSd: Profile Of Mood States – depression part; STAIs: State and Trait Anxiety Inventory – state part; STAIt: State and Trait Anxiety Inventory – trait part. Country abbreviations according to ISO 3166-1 decoding table.

Figure 4. Subthalamic stimulation *versus* comparators forest-plot. Depression and anxiety comparison results following subthalamic stimulation *versus* comparison groups. Data was grouped and analyzed by psychometric instrument and sorted by ascending follow-up time. Effect size and 95% confidence interval are presented for each sample. * Only postoperative evaluation.

Abbreviations: AMDP-AT: Association for Methodology and Documentation in Psychiatry – anxiety part; BAI: Beck Anxiety Inventory; BDI: Beck Depression Inventory; BSIa: Brief Symptom Inventory – anxiety part; BSId: Brief Symptom Inventory – depression part; GDS: Geriatric Depression Scales; HDRS: Hamilton Depression Rating Scale; POMSd: Profile Of Mood States – depression part; STAIs: State and Trait Anxiety Inventory – state part; STAIt: State and Trait Anxiety Inventory – trait part; ES: Eligible for Surgery control group; BMT: Best Medical Treatment control group; GPi: Globus Pallidus internum comparison group. Country abbreviations according to ISO 3166-1 decoding table.

Figure 5. Anxiety psychometric scales forest-plot (STN-DBS). Anxiety assessment results following subthalamic stimulation (STN-DBS) with data grouped and analyzed by psychometric instrument and sorted by ascending follow-up time. Effect size and 95% confidence interval are presented for each sample.

Abbreviations: AMDP-AT: Association for Methodology and Documentation in Psychiatry – anxiety part; BAI: Beck Anxiety Inventory; BAS: Brief Scale for Anxiety; HADa: Hospital Anxiety and Depression scale – anxiety part; HAMA: Hamilton Anxiety scale; SCL90Ra: Symptom CheckList 90 Revised; STAIs: State and Trait Anxiety Inventory – state part; STAIt: State and Trait Anxiety Inventory – trait part; Zunga: Zung self-rating anxiety scale. Country abbreviations according to ISO 3166-1 decoding table.

Figure 1:

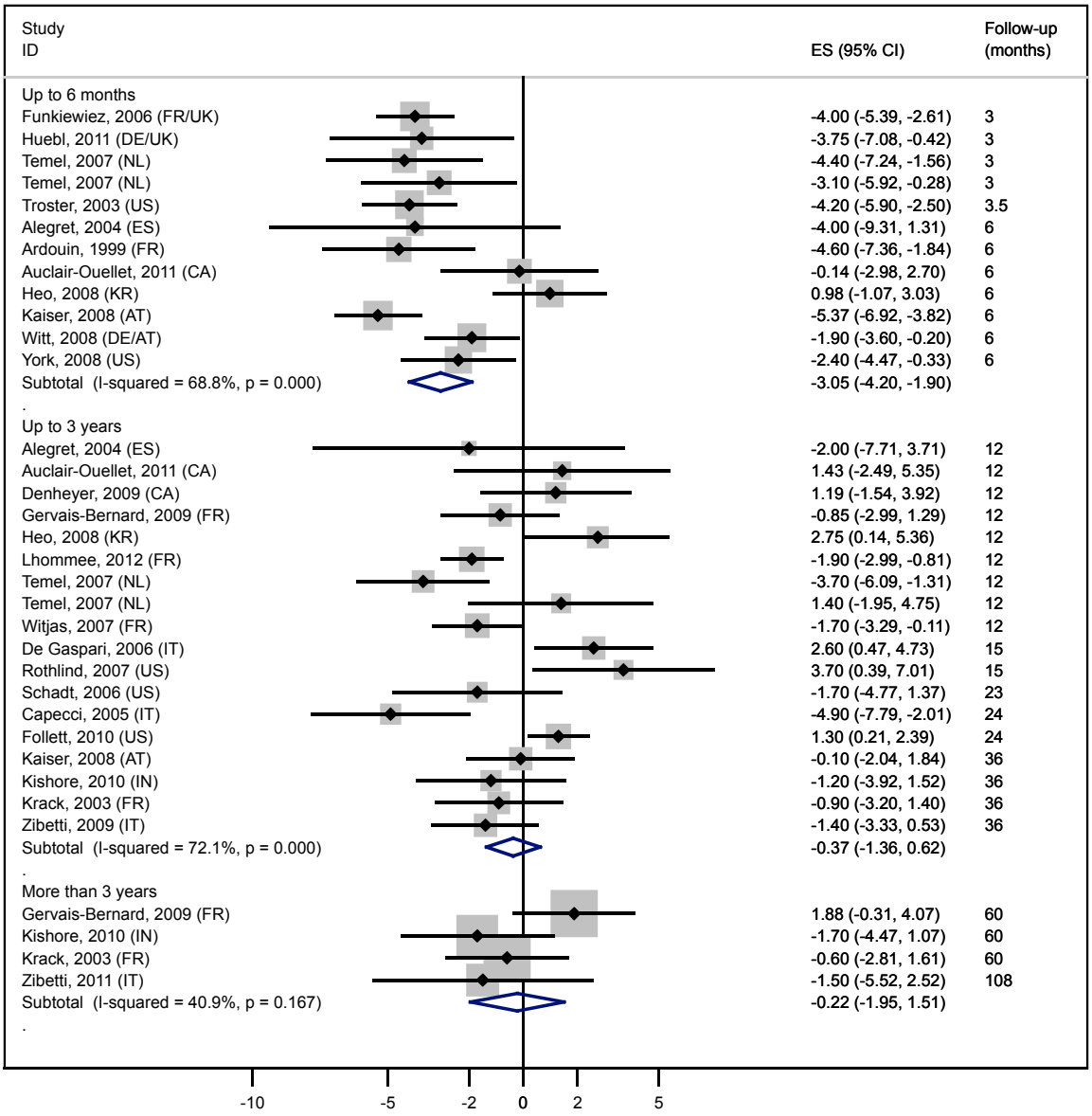

Study ID
ES (95% CI)
Follow-up (months)
Up to 6 months
Funkiewiez, 2006 (FR/UK) -4.00 (-5.39, -2.61) 3
Huebl, 2011 (DE/UK) -3.75 (-7.08, -0.42) 3
Temel, 2007 (NL) -4.40 (-7.24, -1.56) 3
Temel, 2007 (NL) -3.10 (-5.92, -0.28) 3
Troster, 2003 (US) -4.20 (-5.90, -2.50) 3.5
Alegret, 2004 (ES) -4.00 (-9.31, 1.31) 6
Ardouin, 1999 (FR) -4.60 (-7.36, -1.84) 6
Auclair-Ouellet, 2011 (CA) -0.14 (-2.98, 2.70) 6
Heo, 2008 (KR) 0.98 (-1.07, 3.03) 6
Kaiser, 2008 (AT) -5.37 (-6.92, -3.82) 6
Witt, 2008 (DE/AT) -1.90 (-3.60, -0.20) 6
York, 2008 (US) -2.40 (-4.47, -0.33) 6
Subtotal (I-squared = 68.8%, p = 0.000) -3.05 (-4.20, -1.90)
Up to 3 years
Alegret, 2004 (ES) -2.00 (-7.71, 3.71) 12
Auclair-Ouellet, 2011 (CA) 1.43 (-2.49, 5.35) 12
Denheyer, 2009 (CA) 1.19 (-1.54, 3.92) 12
Gervais-Bernard, 2009 (FR) -0.85 (-2.99, 1.29) 12
Heo, 2008 (KR) 2.75 (0.14, 5.36) 12
Lhommee, 2012 (FR) -1.90 (-2.99, -0.81) 12
Temel, 2007 (NL) -3.70 (-6.09, -1.31) 12
Temel, 2007 (NL) 1.40 (-1.95, 4.75) 12
Witjas, 2007 (FR) -1.70 (-3.29, -0.11) 12
De Gaspari, 2006 (IT) 2.60 (0.47, 4.73) 15
Rothlind, 2007 (US) 3.70 (0.39, 7.01) 15
Schadt, 2006 (US) -1.70 (-4.77, 1.37) 23
Capecci, 2005 (IT) -4.90 (-7.79, -2.01) 24
Follett, 2010 (US) 1.30 (0.21, 2.39) 24
Kaiser, 2008 (AT) -0.10 (-2.04, 1.84) 36
Kishore, 2010 (IN) -1.20 (-3.92, 1.52) 36
Krack, 2003 (FR) -0.90 (-3.20, 1.40) 36
Zibetti, 2009 (IT) -1.40 (-3.33, 0.53) 36
Subtotal (I-squared = 72.1%, p = 0.000) -0.37 (-1.36, 0.62)
More than 3 years
Gervais-Bernard, 2009 (FR) 1.88 (-0.31, 4.07) 60
Kishore, 2010 (IN) -1.70 (-4.47, 1.07) 60
Krack, 2003 (FR) -0.60 (-2.81, 1.61) 60
Zibetti, 2011 (IT) -1.50 (-5.52, 2.52) 108
Subtotal (I-squared = 40.9%, p = 0.167) -0.22 (-1.95, 1.51)
-10
-5
-2
0
2
5

Figure 2:

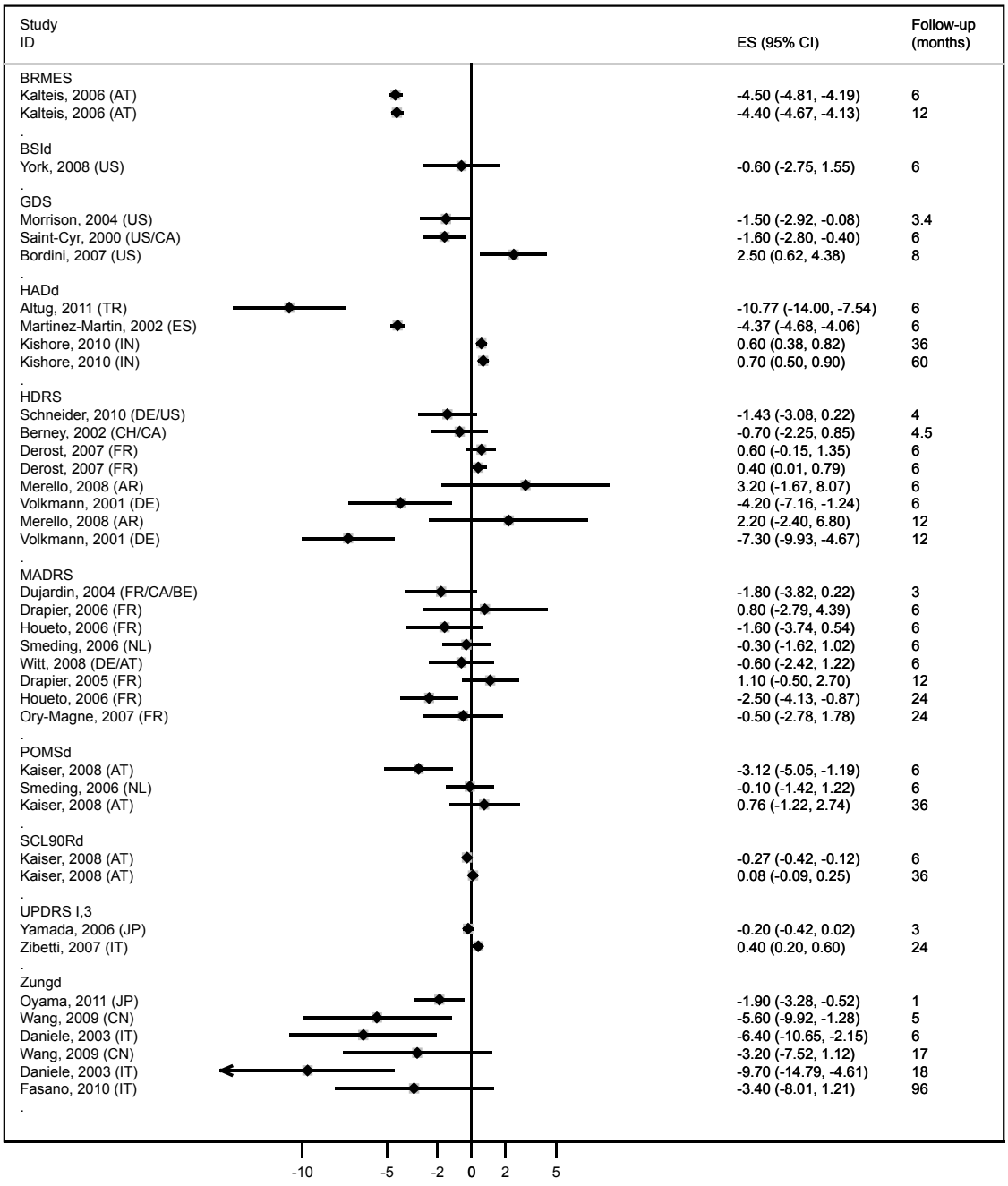

Study ID
ES (95% CI)
Follow-up (months)
BRMES
Kalteis, 2006 (AT) -4.50 (-4.81, -4.19) 6
Kalteis, 2006 (AT) -4.40 (-4.67, -4.13) 12
BSId
York, 2008 (US) -0.60 (-2.75, 1.55) 6
GDS
Morrison, 2004 (US) -1.50 (-2.92, -0.08) 3.4
Saint-Cyr, 2000 (US/CA) -1.60 (-2.80, -0.40) 6
Bordini, 2007 (US) 2.50 (0.62, 4.38) 8
HADd
Altug, 2011 (TR) -10.77 (-14.00, -7.54) 6
Martinez-Martin, 2002 (ES) -4.37 (-4.68, -4.06) 6
Kishore, 2010 (IN) 0.60 (0.38, 0.82) 36
Kishore, 2010 (IN) 0.70 (0.50, 0.90) 60
HDRS
Schneider, 2010 (DE/US) -1.43 (-3.08, 0.22) 4
Berney, 2002 (CH/CA) -0.70 (-2.25, 0.85) 4.5
Derost, 2007 (FR) 0.60 (-0.15, 1.35) 6
Derost, 2007 (FR) 0.40 (0.01, 0.79) 6
Merello, 2008 (AR) 3.20 (-1.67, 8.07) 6
Volkmann, 2001 (DE) -4.20 (-7.16, -1.24) 6
Merello, 2008 (AR) 2.20 (-2.40, 6.80) 12
Volkmann, 2001 (DE) -7.30 (-9.93, -4.67) 12
MADRS
Dujardin, 2004 (FR/CA/BE) -1.80 (-3.82, 0.22) 3
Drapier, 2006 (FR) 0.80 (-2.79, 4.39) 6
Houeto, 2006 (FR) -1.60 (-3.74, 0.54) 6
Smeding, 2006 (NL) -0.30 (-1.62, 1.02) 6
Witt, 2008 (DE/AT) -0.60 (-2.42, 1.22) 6
Drapier, 2005 (FR) 1.10 (-0.50, 2.70) 12
Houeto, 2006 (FR) -2.50 (-4.13, -0.87) 24
Ory-Magne, 2007 (FR) -0.50 (-2.78, 1.78) 24
POMSd
Kaiser, 2008 (AT) -3.12 (-5.05, -1.19) 6
Smeding, 2006 (NL) -0.10 (-1.42, 1.22) 6
Kaiser, 2008 (AT) 0.76 (-1.22, 2.74) 36
SCL90Rd
Kaiser, 2008 (AT) -0.27 (-0.42, -0.12) 6
Kaiser, 2008 (AT) 0.08 (-0.09, 0.25) 36
UPDRS I,3
Yamada, 2006 (JP) -0.20 (-0.42, 0.02) 3
Zibetti, 2007 (IT) 0.40 (0.20, 0.60) 24
Zungd
Oyama, 2011 (JP) -1.90 (-3.28, -0.52) 1
Wang, 2009 (CN) -5.60 (-9.92, -1.28) 5
Daniele, 2003 (IT) -6.40 (-10.65, -2.15) 6
Wang, 2009 (CN) -3.20 (-7.52, 1.12) 17
Daniele, 2003 (IT) -9.70 (-14.79, -4.61) 18
Fasano, 2010 (IT) -3.40 (-8.01, 1.21) 96
-10
-5
-2
0
2
5

Figure 3:

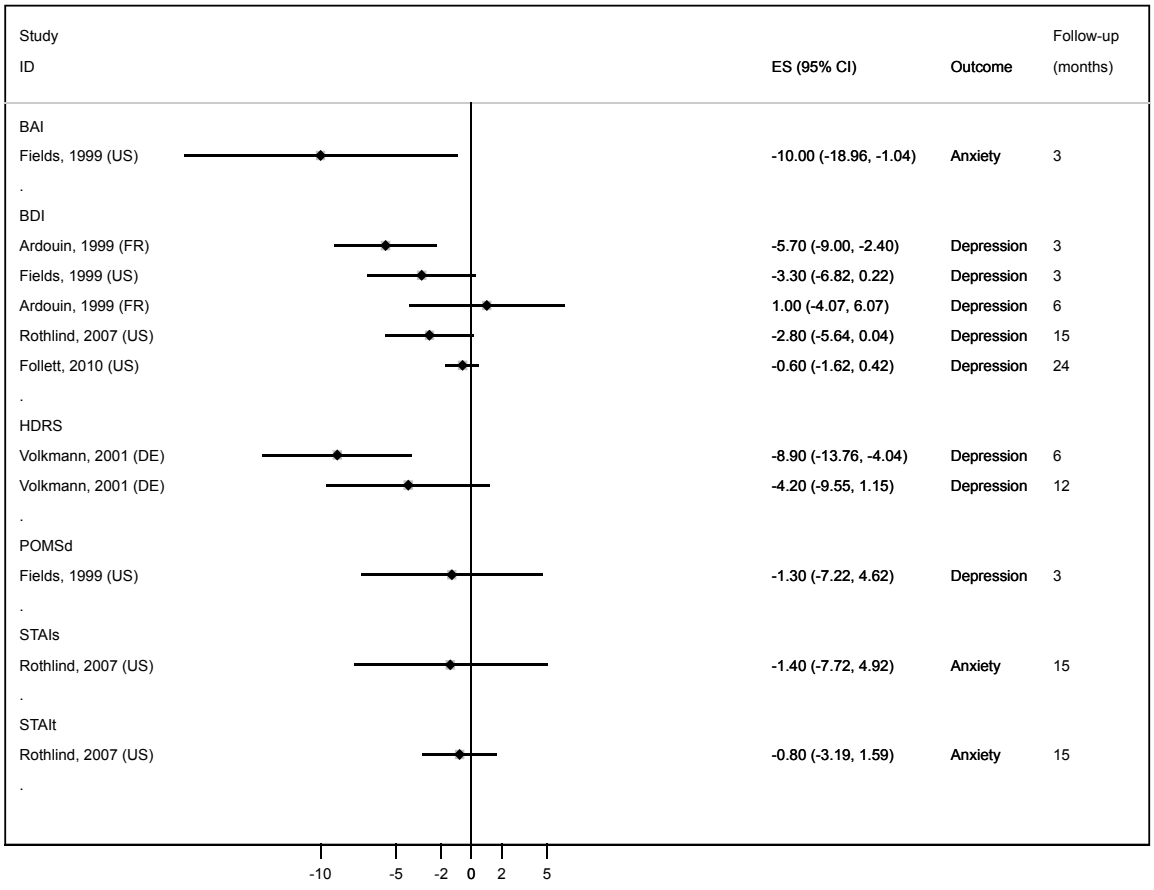

Study ID
ES (95% CI)
Outcome
Follow-up (months)
BAI
Fields, 1999 (US)
-10.00 (-18.96, -1.04)
Anxiety
3
BDI
Ardouin, 1999 (FR)
-5.70 (-9.00, -2.40)
Depression
3
Fields, 1999 (US)
-3.30 (-6.82, 0.22)
Depression
3
Ardouin, 1999 (FR)
1.00 (-4.07, 6.07)
Depression
6
Rothlind, 2007 (US)
-2.80 (-5.64, 0.04)
Depression
15
Follett, 2010 (US)
-0.60 (-1.62, 0.42)
Depression
24
HDRS
Volkmann, 2001 (DE)
-8.90 (-13.76, -4.04)
Depression
6
Volkmann, 2001 (DE)
-4.20 (-9.55, 1.15)
Depression
12
POMSd
Fields, 1999 (US)
-1.30 (-7.22, 4.62)
Depression
3
STAIs
Rothlind, 2007 (US)
-1.40 (-7.72, 4.92)
Anxiety
15
STAIt
Rothlind, 2007 (US)
-0.80 (-3.19, 1.59)
Anxiety
15
-10
-5
-2
0
2
5

Figure 4:

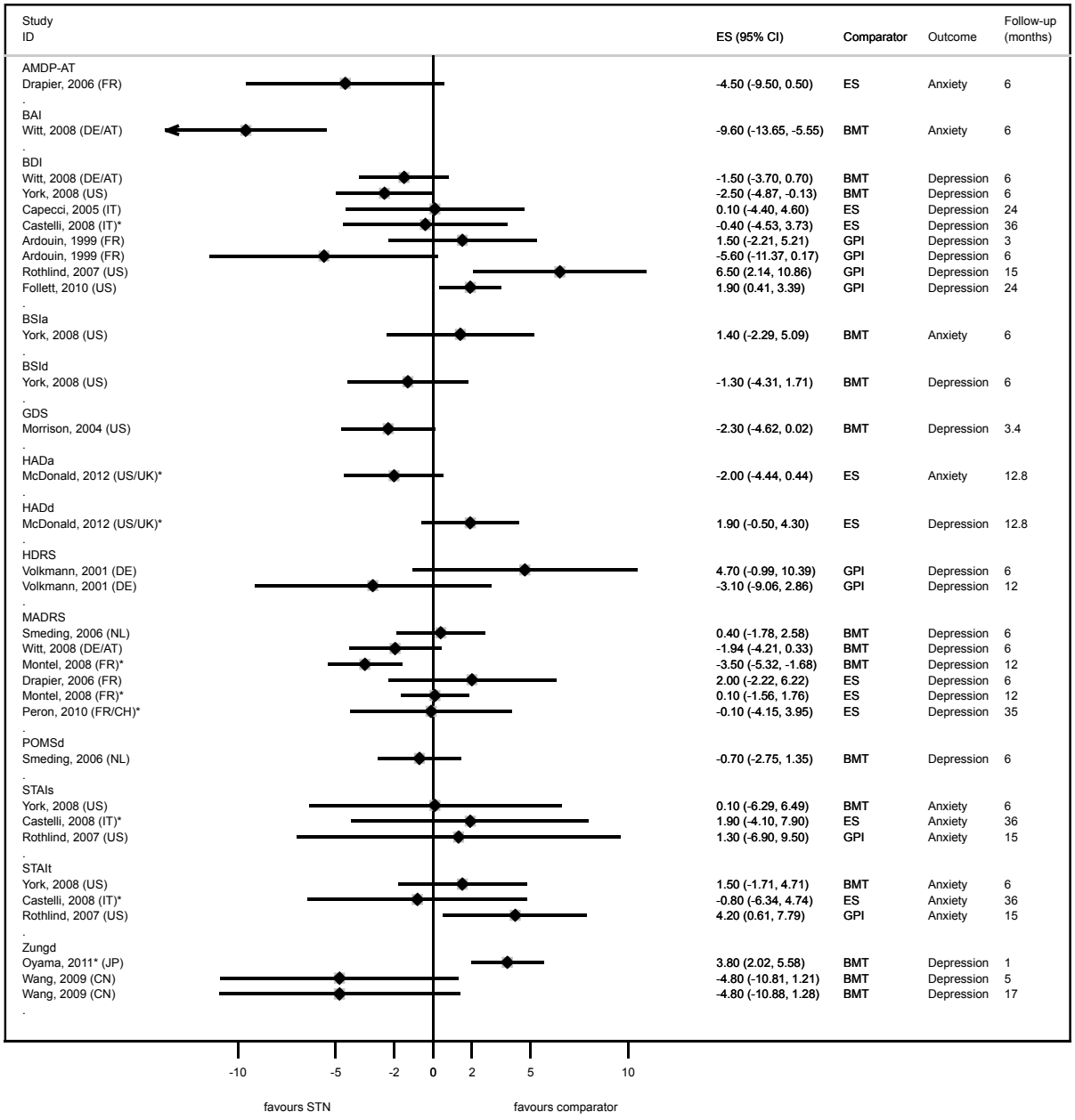
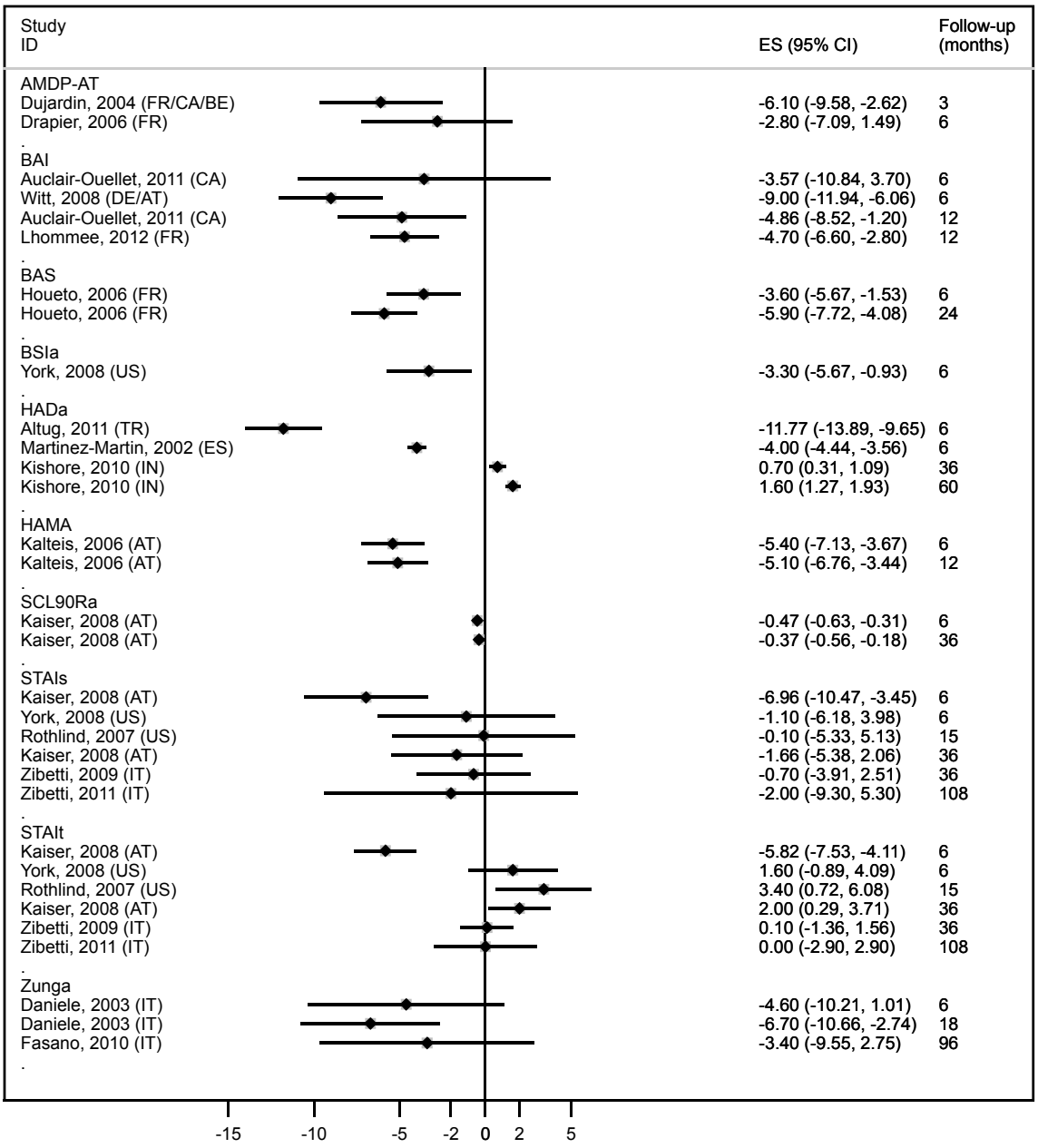

Study ID
ES (95% CI)
Comparator
Outcome
Follow-up (months)
AMDP-AT
Drapier, 2006 (FR) -4.50 (-9.50, 0.50) ES Anxiety 6
BAI
Witt, 2008 (DE/AT) -9.60 (-13.65, -5.55) BMT Anxiety 6
BDI
Witt, 2008 (DE/AT) -1.50 (-3.70, 0.70) BMT Depression 6
York, 2008 (US) -2.50 (-4.87, -0.13) BMT Depression 6
Capecci, 2005 (IT) 0.10 (-4.40, 4.60) ES Depression 24
Castelli, 2008 (IT)* -0.40 (-4.53, 3.73) ES Depression 36
Ardouin, 1999 (FR) 1.50 (-2.21, 5.21) GPI Depression 3
Ardouin, 1999 (FR) -5.60 (-11.37, 0.17) GPI Depression 6
Rothlind, 2007 (US) 6.50 (2.14, 10.86) GPI Depression 15
Follett, 2010 (US) 1.90 (0.41, 3.39) GPI Depression 24
BSIa
York, 2008 (US) 1.40 (-2.29, 5.09) BMT Anxiety 6
BSId
York, 2008 (US) -1.30 (-4.31, 1.71) BMT Depression 6
GDS
Morrison, 2004 (US) -2.30 (-4.62, 0.02) BMT Depression 3.4
HADa
McDonald, 2012 (US/UK)* -2.00 (-4.44, 0.44) ES Anxiety 12.8
HADd
McDonald, 2012 (US/UK)* 1.90 (-0.50, 4.30) ES Depression 12.8
HDRS
Volkmann, 2001 (DE) 4.70 (-0.99, 10.39) GPI Depression 6
Volkmann, 2001 (DE) -3.10 (-9.06, 2.86) GPI Depression 12
MADRS
Smeding, 2006 (NL) 0.40 (-1.78, 2.58) BMT Depression 6
Witt, 2008 (DE/AT) -1.94 (-4.21, 0.33) BMT Depression 6
Montel, 2008 (FR)* -3.50 (-5.32, -1.68) BMT Depression 12
Drapier, 2006 (FR) 2.00 (-2.22, 6.22) ES Depression 6
Montel, 2008 (FR)* 0.10 (-1.56, 1.76) ES Depression 12
Peron, 2010 (FR/CH)* -0.10 (-4.15, 3.95) ES Depression 35
POMSd
Smeding, 2006 (NL) -0.70 (-2.75, 1.35) BMT Depression 6
STAIs
York, 2008 (US) 0.10 (-6.29, 6.49) BMT Anxiety 6
Castelli, 2008 (IT)* 1.90 (-4.10, 7.90) ES Anxiety 36
Rothlind, 2007 (US) 1.30 (-6.90, 9.50) GPI Anxiety 15
STAIt
York, 2008 (US) 1.50 (-1.71, 4.71) BMT Anxiety 6
Castelli, 2008 (IT)* -0.80 (-6.34, 4.74) ES Anxiety 36
Rothlind, 2007 (US) 4.20 (0.61, 7.79) GPI Anxiety 15
Zungd
Oyama, 2011* (JP) 3.80 (2.02, 5.58) BMT Depression 1
Wang, 2009 (CN) -4.80 (-10.81, 1.21) BMT Depression 5
Wang, 2009 (CN) -4.80 (-10.88, 1.28) BMT Depression 17
-10
-5
-2
0
2
5
10
favours STN
favours comparator

Figure 5:


Study ID
ES (95% CI)
Follow-up (months)
AMDP-AT
Dujardin, 2004 (FR/CA/BE) -6.10 (-9.58, -2.62) 3
Drapier, 2006 (FR) -2.80 (-7.09, 1.49) 6
BAI
Auclair-Ouellet, 2011 (CA) -3.57 (-10.84, 3.70) 6
Witt, 2008 (DE/AT) -9.00 (-11.94, -6.06) 6
Auclair-Ouellet, 2011 (CA) -4.86 (-8.52, -1.20) 12
Lhommee, 2012 (FR) -4.70 (-6.60, -2.80) 12
BAS
Houeto, 2006 (FR) -3.60 (-5.67, -1.53) 6
Houeto, 2006 (FR) -5.90 (-7.72, -4.08) 24
BSIa
York, 2008 (US) -3.30 (-5.67, -0.93) 6
HADa
Altug, 2011 (TR) -11.77 (-13.89, -9.65) 6
Martinez-Martin, 2002 (ES) -4.00 (-4.44, -3.56) 6
Kishore, 2010 (IN) 0.70 (0.31, 1.09) 36
Kishore, 2010 (IN) 1.60 (1.27, 1.93) 60
HAMA
Kalteis, 2006 (AT) -5.40 (-7.13, -3.67) 6
Kalteis, 2006 (AT) -5.10 (-6.76, -3.44) 12
SCL90Ra
Kaiser, 2008 (AT) -0.47 (-0.63, -0.31) 6
Kaiser, 2008 (AT) -0.37 (-0.56, -0.18) 36
STAIs
Kaiser, 2008 (AT) -6.96 (-10.47, -3.45) 6
York, 2008 (US) -1.10 (-6.18, 3.98) 6
Rothlind, 2007 (US) -0.10 (-5.33, 5.13) 15
Kaiser, 2008 (AT) -1.66 (-5.38, 2.06) 36
Zibetti, 2009 (IT) -0.70 (-3.91, 2.51) 36
Zibetti, 2011 (IT) -2.00 (-9.30, 5.30) 108
STAIt
Kaiser, 2008 (AT) -5.82 (-7.53, -4.11) 6
York, 2008 (US) 1.60 (-0.89, 4.09) 6
Rothlind, 2007 (US) 3.40 (0.72, 6.08) 15
Kaiser, 2008 (AT) 2.00 (0.29, 3.71) 36
Zibetti, 2009 (IT) 0.10 (-1.36, 1.56) 36
Zibetti, 2011 (IT) 0.00 (-2.90, 2.90) 108
Zunga
Daniele, 2003 (IT) -4.60 (-10.21, 1.01) 6
Daniele, 2003 (IT) -6.70 (-10.66, -2.74) 18
Fasano, 2010 (IT) -3.40 (-9.55, 2.75) 96
-15
-10
-5
-2
0
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5

Movement Disorders

Edited By: C. Warren Olanow, MD, FRCPC andJose A. Obeso, MD, PhD

Impact Factor: 4.505

ISI Journal Citation Reports © Ranking: 2011: 24/192 (Clinical Neurology)

Online ISSN: 1531-8257

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Sample References

- Journal article:
  1. Krack P, Benzzzouz A, Pollak P, et al. Treatment of tremor in Parkinson's disease by Subthalamic nucleus stiumulation. Mov Disord 1998; 13: 907-914.
- Book:
  2.Fahn S, Jankovic J, editors. Principles and Practice of Movement Disorders, Philadelphia, Churchill Livingstone, 2010, pp 96.
- Chapter in a book:
  3. Olanow CW. Hpyerkinetic Movement Disorders. In: Fauci A, Braunwald E, Kasper D, Hauser S, Longo D, Jameson JL, Loscalzo J. Eds. Harrison's Textbook of Medicine 17th edition. 2008; p2560-2565.

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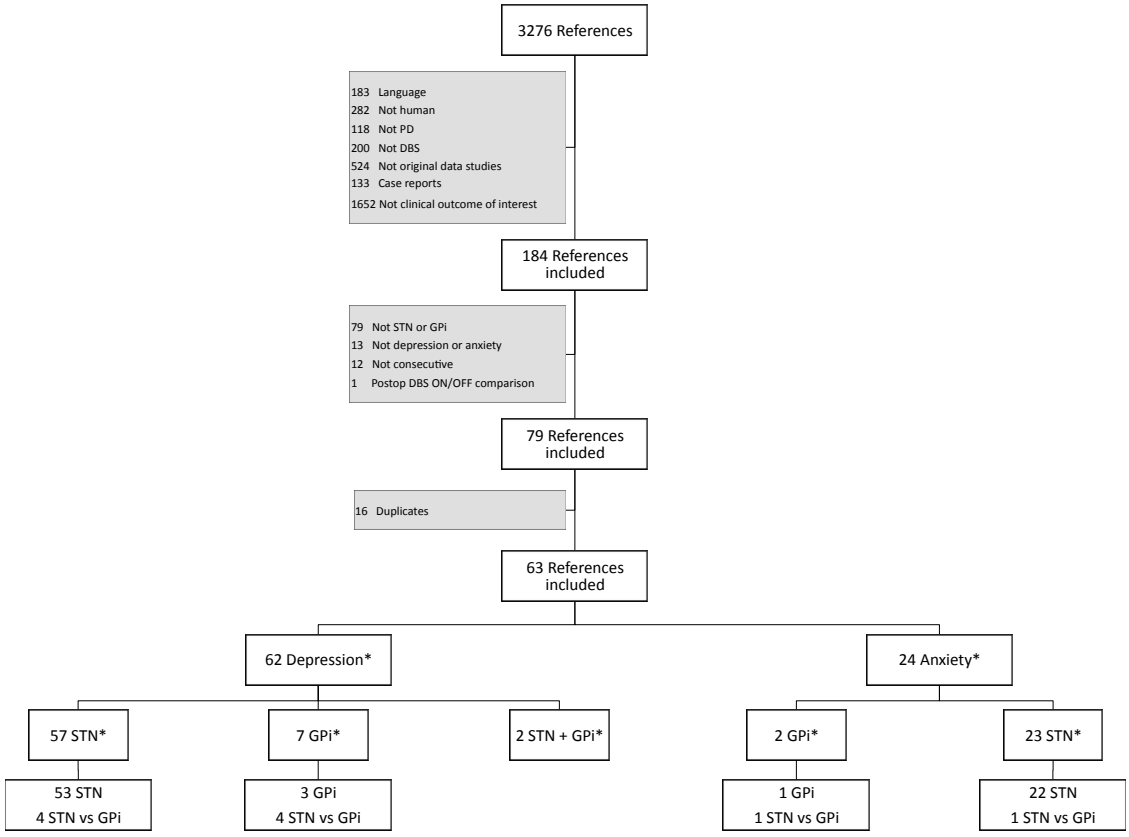
Appendix 1. Systematic review flow-chart



Systematic review approach is outlined with respective proportion of excluded references attributed to each criterion. Literature distribution by psychiatric outcome and surgical target is also presented. * The same reference might be contained in more than one group.

Abbreviations: PD: Parkinson's Disease; DBS: Deep Brain Stimulation; STN: SubThalamic Nucleus; GPi: Globus Pallidus internum; STN + GPI: studies with data not discriminated regarding both targets; STN vs GPi: studies with comparison between both targets.

Appendix 2. Included references details

	Assessment Scales																														
	Depression															Anxiety															
Author, Year (Country)	Ardouind	BDI	BRMES	BSId	GDS	HADd	HDRS	IOWAd	MADRS	MINId	NMSQuestd	POMSd	SCL90Rd	UPDRS 1,3	Zungd	AMDP-AT	Ardouina	BA	BAS	BSIa	HADa	HAMA	IOWAa	MINIa	NMSQuesta	SCL90Ra	STAIs	STAIt	Zunga	STN	GPI	Follow-up	Follow-up time	Comparator
Alegret, 2004 (ES) (a)		x																											✓		✓	6m, 1y	
Altug, 2011 (TR) (a,e)						x															x								✓		✓	3m, 6m	
Auclair-Ouellet, 2011 (CA) (a,l)		x																x											✓		✓	6m, 1y	
Berney, 2002 (CH/CA) (a,h)							x		x(d)																				✓		✓	3-6m	
Bordini, 2007 (US) (a)					x																								✓		✓	6m	
Daniele, 2003 (IT) (a,e,F)															x													x	✓		✓	4m, 6m, 1y, 18m	
De Gaspari, 2006 (IT) (a)		x																											✓		✓	15m	
Denheyer, 2009 (CA) (a)		x																											✓		✓	16m	
Derost, 2007 (FR) (a,g,i)							x																						✓		✓	6m	
Drapier, 2005 (FR) (a)									x																				✓		✓	1y	
Dujardin, 2004 (FR/CA/BE) (a,A)									x							x													✓		✓	3m	
Fasano, 2010 (IT) (a)															x													x	✓		✓	8y	
Funkiewiez, 2006 (FR/UK) (a,i,o)		x																											✓		✓	3m	
Gervais-Bernard, 2009 (FR) (a)		x																											✓		✓	1y, 5y	
Heo, 2008 (KR) (a)		x																											✓		✓	6m, 1y	
Houeto, 2002 (FR)								x(J)		x(c)													x(J)	x(c)					✓		✓	19m	
Houeto, 2006 (FR) (a)									x										x										✓		✓	6m, 2y	
Huebl, 2011 (DE/UK) (n)		x																											✓		✓	3m	
Kaiser, 2008 (AT) (a,e,h,D)		x										x	x													x	x	x	✓		✓	3m, 6m, 1y, 3y	
Kalteis, 2006 (AT) (a,e,D)		x	x									x	x									x				x	x	x	✓		✓	3w, 9w, 3m, 6m, 1y	
Kishore, 2010 (IN) (a,e)		x				x															x								✓		✓	1y, 3y, 5y	
Krack, 2003 (FR) (a)		x																											✓		✓	1y, 3y, 5y	
Krause, 2004 (DE) (k)														x															✓		✓	30m	
Lhommée, 2012 (FR) (a,j,l)	x(c)	x								x(c)							x(c)	x						x(c)					✓		✓	1y	
Martínez-Martín, 2002 (ES) (a)						x															x								✓		✓	6m	
Merello, 2008 (AR) (a)							x																						✓		✓	6m, 1y	
Nazzaro, 2011 (US) (c)											x														x				✓		✓	1y	
Ory-Magne, 2007 (FR) (a,e)									x																				✓		✓	1y, 2y	
Perozzo, 2001 (IT) (d)		x																									x	x	✓		✓	6m	
Perriol, 2006 (FR) (c)									x																				✓		✓	1y	
Saint-Cyr, 2000 (US/CA) (a,f)					x																								✓		✓	6m	
Schadt, 2006 (US) (a,h,m)		x																											✓		✓	23m	
Schneider, 2010 (DE/US) (a,e,f)							x																						✓		✓	5-10d, 18-24d, 3-4m	
Schoenberg, 2008 (US) (d)																											x	x	✓		✓	5m	
Simuni, 2002 (US) (d)					x																								✓		✓	6m	
Temel, 2007 (NL) (b,g)		x																											✓		✓	3m, 1y	
Tröster, 2003 (US) (a)		x																											✓		✓	3,5m	
Witjas, 2007 (FR) (a)		x																											✓		✓	1y	
Yamada, 2006 (JP) (a,j)														x															✓		✓	3m	
Zibetti, 2007 (IT) (a,e)														x															✓		✓	1y, 2y	
Zibetti, 2009 (IT) (a,e,E)		x																									x	x	✓		✓	4m, 1y, 3y	
Zibetti, 2011 (IT) (a,e,E)		x																									x	x	✓		✓	1y, 5y, 9y	
Morrison, 2004 (US) (a,j)					x																								✓		✓	3m	2
Oyama, 2011 (JP) (a,f,O)															x														✓		✓	2-4w	2
Smeding, 2006 (NL) (b)									x			x																	✓		✓	6m	2
Wang, 2009 (CN) (a,e,G,H)							x(C)								x														✓		✓	1w, 2m, 5m, 11m, 17m	2
Witt, 2008 (DE/AT) (b,B)		x							x									x											✓		✓	6m	2
York, 2008 (US) (a)		x		x																x							x	x	✓		✓	6m	2
Capecci, 2005 (IT) (a,e)		x																											✓		✓	1y, 2y	3
Drapier, 2006 (FR) (a,e)									x							x													✓		✓	3m, 6m	3
Péron, 2010 (FR/CH) (a)									x																				✓			35m	1,3
Montel, 2008 (FR) (a)									x	x(c)																			✓			1y	2,3
Castelli, 2008 (IT) (a)		x																									x	x	✓			3y	3
McDonald, 2012 (US/UK) (l)						x															x								✓			1y	3
Fields, 1999 (US) (n,M,N)		x										x						x												✓	✓	3m	
Ghika, 1998 (CH) (d)		x																												✓	✓	3m	
Loher, 2002 (CH/DE) (q)							x																							✓	✓	3m, 1y	
Burchiel, 1999 (US)*		x																											✓	✓	✓	1y	
Weaver, 2009 (US)*		x																											✓	✓	✓	6m	2
Ardouin, 1999 (FR) (a,g,K,L)		x																											✓	✓	✓	3m, 6m	4
Follett, 2010 (US) (a,m,p)		x																											✓	✓	✓	2y	4
Rothlind, 2007 (US) (a)		x																									x	x	✓	✓	✓	15m	4
Volkmann, 2001 (DE) (a)							x																						✓	✓	✓	6m, 1y	4

Psychometric instruments used are highlighted with "x". Stimulation target is marked with "✓" in "STN" and/or "GPi" columns. Follow-up studies have "✓" in the respective column and comparison studies are codified by 1 to 4 so different comparators can be

distinguished. Grey shading denotes references excluded from analysis (non-comparable data).

Notes: 1 to 4 corresponds to comparators coding; 1: healthy control group, 2: medical treatment control group, 3 eligible for surgery control group and 4: GPi comparison group; * references with STN and GPi data not discriminated: no further analysis; (a) original data is pre M(SD) and post M(SD): changeM calculated as (postM - preM); changeSD calculated as √ [(preSD2 + posSD2 – 2 x r x preSD x posSD) / n]; (b) original data is pre M(SD) and change M(SD); (c) original data not quantitative/comparable (percentage of patients): no further analysis; (d) original data not quantitative/comparable (qualitative description): no further analysis; (e) within each period of time, the longest follow-up was selected for the analysis; (f) "x to y months" type follow-up: y months assumed; (g) original data reported by groups: separately considered for the analysis; (h) original data reported on total sample and by groups: total sample considered; (i) SD calculated from SE as (SE x √n); (j) original data reported in on and off state: only on considered; (k) original data not quantitative/comparable (no dispersion measure): no further analysis; (l) mean (SD) assumed; (m) SD calculated from 95% CI as [(upper limit - lower limit) / 3.92] x √n; (n) original data reported individually: preM(SD) and changeM(SD) calculated; (o) graphical data; (p) intention-to-treat analysis; (q) original data not quantitative/comparable (percentage of change): no further analysis; (A) cognitive outcomes compared with control group; depression and anxiety assessed only in patients; so, follow-up STN-DBS study design assumed; (B) "positive change scores indicate clinical improvement; data are (...) mean (SD) (...) for changes between baseline (before DBS) and 6 months": – changeM assumed; (C) HDRS not

consecutively assessed: "depression was evaluated (...) using the Self-Rating Depression Scale (...); every patient whose SDS score showed a mild depression, or more, was evaluated again (...) using the Hamilton Depression Scale"; (D) partial duplicates: BDI, POMSd, STAIs, STAIt, SCL-90-Rd and SCL-90-Ra data from Kaiser, 2008; BRMES and HAMA data from Kalteis, 2006; (E) partial duplicates: 3 years follow-up data from Zibetti, 2009; 9 years follow-up data from Zibetti, 2011 (and the respective preoperative data for each one); (F) data from n=20 (whole sample) and from n=9 (18 months follow up sample); evaluation moments at 3, 6, 12 and 18 months; n=20 preoperative data considered for short-term follow-up analysis; n=9 preoperative data considered for mid-term follow-up analysis; (G) stimulation device was turned on 4 weeks after the surgery: postoperative moments converted to post-DBS moments by subtracting 1 month; (H) "depression severity index" = "accumulative scores of each item"/"maximum scores of the scale": mean x 80 and SD x 80 assumed; (I) "the assessments took place (...) 12 months (...) later, with the exception of the cognitive status, which was controlled 3 months after surgery"; "outcome measures" = "motor function" + "cognitive status" + "psychiatric history" + "mood and behavioral modifications: ardouin scale" + "acute non-motor fluctuations": 1 year follow up assumed to mood evaluation; (J) results separated by groups "identical", "ameliorated" and "aggravated": not comparable with other studies; (K) Partial duplicate: 4 groups: STN *versus* GPI and Paris *versus* Grenoble: GPI in Grenoble, GPI *versus* STN comparison in Grenoble, STN in Paris, GPI in Paris and GPI *versus* STN comparison in Paris included; STN in Grenoble duplicated; (L) 4 groups: STN *versus* GPI and Paris *versus* Grenoble: only 57 in a total of 62 patients performed BDI assessment and the distribution by groups was not indicated: total n assumed for each group. (M) staged DBS; evaluation times were "1 month before first surgery, 2 months following first

surgery (unilateral), and 3 months following second surgery (bilateral)": 3 months follow-up assumed; (N) "Test-retest interval was about 3 months between baseline and post-unilateral electrode placement evaluation, and 4 months between post-unilateral and post-bilateral electrode placement evaluations. This occurred with the exception of one patient who on separate occasions had the lead and pulse generator repositioned following bilateral operation, resulting in a 22-month lapse between neuropsychological assessments after first and second DBS electrode placement.": global 3 months follow-up assumed; (O) pre- and postoperative evaluations performed in patients group; only 1 evaluation in control group: postoperative cross-sectional analysis assumed.

Test-retest coefficient (r) was 0,66 for BAI[79], 0,64 (short term) and 0,75 (mid- and long-term) for BDI[77], 0,79 for BSIa[81], 0,84 for BSId[81], 0,94 for GDS[80], 0,98 for HADa[84], 0,99 for HADd[84], 0,87 for HDRS[75], 0,56 for MADRS[76], 0,4 for STAIs[86], 0,86 for STAIt[86] and 0,651 for UPDRS I,3[82]. 0,98 assumed for BRMES[83]. 0,75 assumed for POMSd[85]. Conservative value of 0,56 was assumed for SCL90Rd and Zungd. Conservative value of 0,4 was assumed for AMDP-AT, BAS, HAMA, SCL90Ra and Zunga.

Abbreviations: in “follow-up” column, w, m and y refers to weeks, months and years, respectively; pre = preoperative data; post = postoperative data; M = mean; SD = standard deviation; SE = standard error; 95%CI = 95% confidence interval; r = test-retest correlation coefficient; n=sample size; "change" refers to the postop - preop temporal change; AMDP-AT: association for methodology and documentation In psychiatry, anxiety part; Ardouina and Ardouind: “anxiety” and “depressive mood” items of the Ardouin scale, respectively; BAI: Beck anxiety inventory; BAS: brief scale for anxiety; BDI: Beck depression inventory; BRMES: Bech-Rafaelsen Melancholia

Scale; BSIa and BSId: anxiety and depression scales of the brief symptom inventory, respectively; COMP: comparison study; FU: follow-up study; GDS: geriatric depression scale; GPi: globus pallidus, pars interna; HADa and HADd: anxiety and depression parts of the hospital anxiety and depression scale, respectively; HAMA: Hamilton anxiety scale; HDRS: Hamilton depression rating scale; IOWAa and IOWAd: anxiety and depression parts of the IOWA scales of personality change, respectively; MADRS: Montgomery-Asberg depression rating scale; MINIa and MINId: "general anxiety"/"anxiety disorders" and "major depression episode/disorder" items of the "mini international neuropsychiatric interview, respectively; NMSQuesta and NMSQuestd: items "anxiety" and "feeling sad" of the non motor symptom questionnaire, respectively; POMSd: profile of mood states, depression domain; SCL-90-Ra and SCL-90-Rd: anxiety and depression domains of the symptom checklist-90-revised; STAIs and STAIt: state and trait (respectively) anxiety inventory; STN: subthalamic nucleus; UPDRS I,3: unified parkinson's disease rating scale, part I, item 3 "depression"; Zunga and Zungd: Zung self-rating anxiety and depression scales, respectively. Country abbreviations according to ISO 3166-1 decoding table.